CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761164Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication: Yes

Recommendation: Approval

BLA Number: 761164
Assessment Number: 2, addendum
Assessment Date: January 21, 2022

Drug Name/Dosage Form	Enjaymo (sutimlimab-jome) injection (solution)
Strength/Potency	1100 mg/22 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of hemolysis in adult patients with cold agglutinin disease
Applicant/Sponsor	Bioverativ USA Inc. (A Sanofi Company)

Product Overview

Sutimlimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody specific for complement component 1, s subcomponent (C1s) esterase produced in mammalian (Chinese hamster ovary-CHO) cells. Sutimlimab binds to C1s and inhibit the activation of a classical complement pathway, consequently inhibiting the production of membrane attack complex (MAC) that is responsible for red blood cells (RBC) lysis. Sutimlimab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains 1100 mg/22 mL of sutimlimab at concentration of 50 mg/mL with pH of 6.1. Each mL of solution contains 50 mg sutimlimab, 1.13 (b)(4) mg sodium phosphate monobasic monohydrate, 0.48 (b)(4) mg sodium phosphate dibasic heptahydrate, 8.18 (b)(4) mg sodium chloride, 0.2 mg polysorbate 80 and water for injection. The recommended dose for sutimlimab is 6500 mg for patients weighing 39 kg to less than 75 kg, or 7500 mg for patients weighing 75 kg or more administered intravenously once per week for the first two doses followed by every two weeks dosing thereafter.

Quality Assessment Team

Discipline	Assessor	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	James Barlow and Jennifer Kim Xiaoshi Wang	OPQ/OBP OPQ/OBP/DBRRII
Facility	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2
Microbiology	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality) Madushini Dharmasena (microbiology and facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Hamet Toure and Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Assessment Team

Discipline	Assessor	Office/Division
RPM	Maureen DeMar	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH

Pharm/Tox	Shaji Theodore/ Pedro DelValle	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaolei Pan/Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Enjaymo
   b. Trade Name: ENJAYMO™
   c. Non-Proprietary Name/USAN: Sutimlimab
   d. CAS Registry Number: 2049079-64-1
   e. Common Name: Humanized IgG4 monoclonal antibody, anti-(human complementC1s) (humanized mousemonoclonalTNT009γ4-chain) disulfide with humanized mousemonoclonalTN009k-chain, dimer
   f. INN Name: Sutimlimab
   g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   h. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

Submissions Assessed

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761164/SN0043 (Re-submission)	August 5, 2021
STN 761164/SN0045 (Information request (IR) response)	November 9, 2021 (OBP)
STN 761164/SN0052 (IR response for PMR and PMC)	January 11, 2022 (OBP and clinical)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   Refer to the Integrated Quality Assessment (Also referred to as Executive Summary) dated November 6, 2020 for an assessment of Drug Master Files (DMF), which is attached as Appendix 2 in the current Executive Summary addendum, and supporting documents referenced in the original BLA.

3. Consults: None

4. Environmental Assessment:

   Bioverativ USA Inc. claimed a categorical exclusion from the preparation of an environmental assessment for sutimlimab in accordance with 21 CFR 25.31 (c). The claim is based on that sutimlimab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when sutimlimab is exposed to the environment, it would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist.

   The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc. This memo documents the review of BLA resubmission in response to a Complete Response (CR) Letter issued on November 13, 2020. The application was not approved in the first review cycle due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug substance manufacturing facility (b) (4) From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER, did not identify any product quality deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc in the first review cycle. In the BLA resubmission, the Applicant removes the (b) (4) site as the drug substance manufacturing facility but keeps (b) (4) site for quality control testing for both drug substance and drug product. The office of Regulatory Affairs (ORA) led the PLI on (b) (4) site and concluded that data integrity issues identified at (b) (4) site related to the testing results submitted in BLA 761164 were resolved, and (b) (4) site as a quality control testing facility has acceptable CGMP compliance status. Therefore, this BLA resubmission is recommended for approval from a facility standpoint, and the Applicant adequately addressed the (b) (4) facility deficiencies communicated in the CR Letter. Additional information is in the primary facility review from the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER. The initial Executive Summary for BLA 761164 resubmission uploaded in DARRTS on January 6, 2022 prior to the ORA led PLI is attached as Appendix 1 in the current Executive Summary addendum.

Manufacturing and control strategy updates made since the first review cycle were included in the response to the CR Letter and reviewed. The product quality information provided in the resubmission do not impact the recommendation of approval for BLA 761164 made by OBP during the first review cycle. The data submitted in the original application and subsequent resubmission are adequate to support the conclusion that the manufacture of Enjaymo (sutimlimab-jome) is well controlled and leads to a product that is pure and potent. Therefore, OPQ recommends that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance:

  (b) (4)

- Drug Product:

(b) (4)

- Fill size and dosage form: 1100 mg/22 mL solution

- Dating period:
  - Drug Product: 18 months at 2-8°C
  - Drug Substance: (b) (4) months at (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release in accordance with 21 CFR 601.2a. Enjaymo (sutimlimab-jome) is a specified product.

C. Benefit/Risk Considerations:

Refer to the Executive Summary memo dated November 6, 2020 for Benefit/Risk Considerations assessed during the first review cycle which is attached as Appendix 2 in the current Executive Summary addendum.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: No

(b) (4)

II. Summary of Quality Assessments:

Refer to the Executive Summary memo dated November 6, 2020 for an assessment of critical quality attributes, risks, lifecycle management, and establishment information which is attached as Appendix 2 in the current Executive Summary addendum. Additional information is in the Product Quality, Microbiology, and Facility primary technical reviews.

Appendix 1

First Approval for Indication: Yes

Recommendation: Pending the final determination of compliance status of the quality control testing site at (b) (4)

BLA 761164
Review Number: 2
Review Date: January 6, 2022

Drug Name/Dosage Form	Enjaymo (sutimlimab-jome) injection (solution)
Strength/Potency	1100 mg/22 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of hemolysis in adult patients with cold agglutinin disease
Applicant	Bioverativ USA Inc. (A Sanofi Company)

Product Overview

Sutimlimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody specific for complement component 1, s subcomponent (C1s) esterase produced in mammalian (Chinese hamster ovary-CHO) cells. Sutimlimab binds to C1s and inhibit the activation of a classical complement pathway, consequently inhibiting the production of membrane attack complex (MAC) that is responsible for red blood cells (RBC) lysis. Sutimlimab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains 1100 mg/22 mL of sutimlimab at concentration of 50 mg/mL with pH of 6.1. Each mL of solution contains 50 mg sutimlimab, 1.13 (b) (4) mg sodium phosphate monobasic monohydrate, 0.48 (b) (4) mg sodium phosphate dibasic heptahydrate, 8.18 (b) (4) mg sodium chloride, 0.2 mg polysorbate 80 and water for injection. The recommended dose for sutimlimab is 6500 mg for patients weighing 39 kg to less than 75 kg, or 7500 mg for patients weighing 75 kg or more administered intravenously once per week for the first two doses followed by every two weeks dosing thereafter.

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	James Barlow and Jennifer Kim Xiaoshi Wang	OPQ/OBP OPQ/OBP/DBRRII
Facility	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2
Microbiology	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality) Madushini Dharmasena (microbiology and facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Hamet Toure and Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Maureen DeMar	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH
Pharm/Tox	Shaji Theodore/ Pedro DelValle	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaolei Pan/Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   i. Proprietary Name: Enjaymo
   j. Trade Name: ENJAYMO™
   k. Non-Proprietary Name/USAN: Sutimlimab
   l. CAS Registry Number: 2049079-64-1
   m. Common Name: Humanized IgG4 monoclonal antibody, anti-(human complementC1s) (humanized mousemonoclonalTNT009γ4-chain) disulfide with humanized mousemonoclonalTN009k-chain, dimer
   n. INN Name: Sutimlimab
   o. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   p. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761164/SN0043 (Re-submission)	August 5, 2021
STN 761164/SN0045 (Information request response)	November 9, 2021 (OBP)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:
   Refer to the Integrated Quality Assessment (Also referred to as Executive Summary) dated November 6, 2020 for an assessment of Drug Master Files (DMF) and supporting documents referenced in the original BLA.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	128190	Parent IND

3. Consults: None

4. Environmental Assessment:

Bioverativ USA Inc. claimed a categorical exclusion from the preparation of an environmental assessment for sutimlimab in accordance with 21 CFR 25.31 (c). The claim is based on that sutimlimab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when sutimlimab is exposed to the environment, it would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

B. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc. is pending the final determination of compliance status of the quality control testing site at (b) (4) FDA assessment of the ability of this facility to conduct quality control tests in compliance with CGMP is required to support approval of the application. This memo documents the review of BLA resubmission in response to a Complete Response (CR) Letter issued on November 13, 2020. The application was not approved in the first review cycle due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of (b) (4) drug substance manufacturing facility (b) (4) From product quality and microbiology perspective, the Office of Biotechnology Products (OBP), OPQ, CDER, and the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER, respectively, did not identify any deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc in the first review cycle. In the BLA resubmission, the Applicant removes the (b) (4) site as the drug substance manufacturing facility but keeps (b) (4) site for quality control testing for both drug substance and drug product. The on-site PLI led by the office of Regulatory Affairs (ORA) will start on (b) (4) The final determination of compliance status of the quality control testing site at (b) (4) is pending on the inspectional outcome.

Manufacturing and control strategy updates made since the first review cycle were included in the response to the CR Letter and reviewed. The product quality information provided in the resubmission does not impact the recommendation of approval for BLA 761164 made by OBP during the first review cycle. The data submitted in the original application and subsequent resubmission are adequate to support the conclusion that the manufacture of Enjaymo (sutimlimab-jome) is well controlled and leads to a product that is pure and potent. Therefore,

OPQ recommends that this product be approved for human use under conditions specified in the package insert.

E. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: (b) (4)
- Drug Product: (b) (4)

- Fill size and dosage form: 1100 mg/22 mL solution
- Dating period:
  - Drug Product: 18 months at 2-8°C
  - Drug Substance: (b) (4) months at (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. Enjaymo (sutimlimab-jome) is a specified product.

F. Benefit/Risk Considerations:

Refer to the Executive Summary memo dated November 6, 2020 for Benefit/Risk Considerations assessed during the first review cycle.

G. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

(b) (4)

(b) (4)

II. Summary of Quality Assessments:

Refer to the Executive Summary memo dated November 6, 2020 for an assessment of critical quality attributes, risks, lifecycle management, and establishment information. Additional information is in the Product Quality, Microbiology, and Facility primary technical reviews.

Appendix 2

First Approval for Indication: Yes

Recommendation: Compete Response

BLA Number: 761164
Review Number: 1
Review Date: November 6, 2020

Drug Name/Dosage Form	Enjaymo (sutimlimab-jome) injection (solution)
Strength/Potency	1100 mg/22 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of hemolysis in adult patients with cold agglutinin disease
Applicant/Sponsor	Bioverativ USA Inc. (A Sanofi Company)

Product Overview

Sutimlimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody specific for complement component 1, s subcomponent (C1s) esterase produced in mammalian (Chinese hamster ovary-CHO) cells. Sutimlimab binds to C1s and inhibit the activation of a classical complement pathway, consequently inhibiting the production of membrane attack complex (MAC) that is responsible for red blood cells (RBC) lysis. Sutimlimab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains 1100 mg/22 mL of sutimlimab at concentration of 50 mg/mL with pH of 6.1. Each mL of solution contains 50 mg sutimlimab, 1.13 (b)(4) mg sodium phosphate monobasic monohydrate, 0.48 (b)(4) mg sodium phosphate dibasic heptahydrate, 8.18 (b)(4) mg sodium chloride, 0.2 mg polysorbate 80 and water for injection. The recommended dose for sutimlimab is 6500 mg for patients weighing 39 kg to less than 75 kg, or 7500 mg for patients weighing 75 kg or more administered intravenously once per week for the first two doses followed by every other week dosing thereafter.

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	Scott Dallas James Barlow Xiaoshi Wang	OPQ/OBP OPQ/OBP OPQ/OBP/DBRRII
Facility	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Microbiology	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Inspection	Viviana Matta (lead) Cyrus Agarabi	OPQ/OPMA/DBM/BMB2 OPQ/OBP/DBRRII
Team Lead	Yan Wang (product quality) Candace Gomez-Broughton (microbiology, DS) Maria (Reyes) Candau-Chacon (microbiology, DP) Peter Qiu (facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII

OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Florence Aisida	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Maureen DeMar/Charlene Wheeler	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH
Pharm/Tox	Shaji Theodore/Lee Elmore	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaolei Pan/Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Yaping Wang/Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   q. Proprietary Name: Enjaymo
   r. Trade Name: ENJAYMO™
   s. Non-Proprietary Name/USAN: Sutimlimab
   t. CAS Registry Number: 2049079-64-1
   u. Common Name: Humanized IgG4 monoclonal antibody, anti-(human complementC1s) (humanized mousemonoclonalTNT009γ4-chain) disulfide with humanized mousemonoclonalTN009k-chain, dimer
   v. INN Name: Sutimlimab
   w. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   x. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761164/SN0001 (Pre-submission)	September 5, 2019 (Non-clinical submission)
STN 761164/SN0001 (Pre-submission)	February 28, 2020 (Clinical submission)
STN 761164/SN0003 (Original submission)	March 13, 2020 (OBP and OPMA)
STN 761164/SN0004 (Quality submission within 30 days for Photostability, temperature excursion and in-use data)	April 10, 2020 (OBP and OPMA)
STN 761164/SN007 (Quality submission for data integrity investigation deviation reports)	May 1, 2020 (OBP and OPMA)
STN 761164/SN0009 (Information request (IR) response)	May 19, 2020 (OPMA)
STN 761164/SN0010 (IR response)	May 28, 2020 (OBP)
STN 761164/SN0013 (IR response)	June 12, 2020 (OBP)
STN 761164/SN0014 (IR response)	July 2, 2020 (OBP)
STN 761164/SN0015 (IR response)	July 9, 2020 (OBP)
STN 761164/SN0016 (IR response)	July 20, 2020 (OBP)
STN 761164/SN0017 (IR response)	July 17, 2020 (OPMA)
STN 761164/SN0018 (IR response)	July 28, 2020 (OBP)
STN 761164/SN0019 (IR response)	August 4, 2020 (OPMA)
STN 761164/SN0020 (IR response)	August 5, 2020 (OBP)
STN 761164/SN0021 (IR response)	August 10, 2020 (OBP)
STN 761164/SN0024 (IR response)	August 31, 2020 (OPMA)
STN 761164/SN0025 (IR response)	September 2, 2020 (OBP)
STN 761164/SN0027 (IR response)	September 15, 2020 (OBP)
STN 761164/SN0028 (IR response)	September 18, 2020 (OPMA)
STN 761164/SN0029 (IR response)	September 25, 2020 (OBP and OPMA)

STN 761164/SN0030 (IR response)	October 1, 2020 (OBP)
STN 761164/SN0032 (IR response)	October 5, 2020 (OBP)
STN 761164/SN0033 (IR response)	October 9, 2020 (OBP)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	3	Adequate	N/A	N/A
	V			2	Adequate	(b) (4)	N/A
	III			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	128190	Parent IND

3. Consults: None

4. Environmental Assessment:

   Bioverativ USA Inc. claimed a categorical exclusion from the preparation of an environmental assessment for sutimlimab in accordance with 21 CFR 25.31 (c). The claim is based on that sutimlimab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when sutimlimab is exposed to the environment, it

would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

C. Recommendation and Conclusion on Approvability:

Recommendation:

This application will not be approved during this assessment cycle due to deficiencies identified for (b) (4) facility. The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug substance manufacturing facility (b) (4) From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER, does not note any product quality deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc at this time. Because the application will not be approved in this cycle, the manufacturing facility issues listed below will be directly communicated to (b) (4) due to (b) (4) is a contract manufacturing organization (CMO). If manufacturing changes are made before the applicant submits their responses to the complete response (CR) deficiencies, additional assessment may be needed during the next assessment cycle.

H. Summary of Complete Response Issues:

The following deficiencies were identified regarding (b) (4) facility which is responsible for sutimlimab DS manufacturing process and quality control for release and stability testing of sutimlimab DS and DP.

A PLI was conducted at the (b) (4) facility in (b) (4). The PLI resulted in a final withhold decision for this BLA.

- Lack of quality oversight
- Significant data integrity concerns and failure to conduct a comprehensive data integrity assessment to ensure the accurate and reliable results submitted to the BLA application

I. Complete Response Letter Draft Language:

During a recent inspection of the (b) (4) facility for this BLA, our field investigator observed objectionable conditions at the facility and conveyed

that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

J. Benefit/Risk Considerations:

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia caused by IgM-induced complement pathway activation. The disease is characterized by the presence of autoantibodies called cold agglutinins (generally IgM isotype and act as potent activators of the complement pathway) that typically bind to the I antigen uniformally present on the surface of all RBCs. Sutimlimab is a humanized IgG4 monoclonal antibody and it specifically targets C1s. Sutimlimab blocks the activity of the C1s esterase, the proximal step in the activation of the classical complement pathway. Inhibition of C1s has been shown to inhibit RBC opsonization and downstream complement activity, protection of RBCs from hemolytic clearance and destruction. There is a high unmet medical need for treatment of hemolysis in CAD which leads to severe symptomatic anemia because no therapies are currently approved for the treatment of patients with CAD.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are sufficiently controlled to result in a consistent and safe product from product quality perspective. In addition, the microbial control and sterility assurance strategy are sufficient to support consistent manufacture of a sterile product from microbiology product quality perspective. The proposed commercial manufactures of sutimlimab DS at (b) (4) and of sutimlimab DP at (b) (4) (b) (4) are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. However, due to the deficiencies identified in the proposed commercial DS manufacturing facility as well as the quality control testing unit at (b) (4) site, the Agency is unable to conclude that the (b) (4) facility is ready for commercial manufacturing and can adequately resolve data integrity issues during the current review cycle for the application. The OBP product quality and immunogenicity assay, OPMA facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

K. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

(b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for Sutimlimab

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Binding to C1s (Potency)	Efficacy	Intrinsic to the molecule, impacted by oxidation and low pH stress	(b) (4)	Characterized by a C1s binding assay (ELISA, (b) (4) Characterized by reduced FcγR and C1q binding affinities
Production of MAC (Potency)	Efficacy	Intrinsic to the molecule		Characterized by a Wieslab complement assay (b) (4)
Inhibition of sheep red blood cell hemolysis (Potency)	Efficacy	Intrinsic to the molecule		Characterized by a cell-based assay (b) (4)
Identity	Efficacy and Safety	Intrinsic to the molecule		N/A
High Molecular Weight (HMW) species/Aggregates (Product related impurity)	Pharmacokinetics (PK), and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low pH, high pH, oxidation reagent stress, metals (b) (4) and light		(b) (4)
LMW species/Fragments (Product related impurity)	Efficacy	Manufacturing process, and exposure to low pH, high pH, heat and oxidation reagent stress,		N/A

		metals (b) (4) and light		
Heavy chain (b) (4)	PK	Manufacturing process and exposure to oxidation reagent stress and photo stress Minimal change is expected on stability due to high temperature and pH stress Significant increased under photo stress	(b) (4)	(b) (4)
High mannose	PK	Bioreactor conditions Minimal change is expected on stability		(b) (4)
Charge variant profile (Acidic variants)	Efficacy, PK/ Pharmacodynamics (PD)	Manufacturing process and exposure to high pH, oxidation reagent stress, metal (b) (4) and light		
Charge variant profile (Basic variants)	Efficacy, PK/PD	Manufacturing process and exposure to heat, low pH, high pH, oxidation reagent stress, metals (b) (4) and light		

B. Drug Substance (Sutimlimab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
(b) (4) Concentration	Efficacy (Product oxidation) and Stability	(b) (4)	(b) (4)	N/A
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	(b) (4) and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (Includes degree of opalescence and color of solution) (General)	Stability	(b) (4) and stability		N/A

Host Cell DNA (Process related impurity)	Safety	Production cell line, bioreactor (b) (4)	(b) (4)	(b) (4)
Host Cell Protein (Process related impurity)	Immunogenicity	Production cell line, bioreactor (b) (4)		
(b) (4) (Process related impurity)	Safety	Purification through the (b) (4)		
Adventitious viruses, endogenous virus (Process related impurity)	Safety	Cell banks, raw materials		
Mycoplasma (Process related impurity)	Safety	Cell banks, raw materials		
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		N/A
(b) (4)	Safety	(b) (4)		Levels are below toxicological concern based on the risk assessment

- Description:
  Sutimlimab is a humanized IgG4 monoclonal antibody (mAb) against C1s. Sutimlimab is produced from a mammalian cell line (CHO) using a (b) (4) process.

Sutimlimab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. Sutimlimab contains a serine-to-proline mutation (S241P) for stabilization of the core-hinge region of the molecule. In addition, sutimlimab contains a leucine-to-glutamic acid mutation (L248E) to reduce Fcγ receptor binding. Sutimlimab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N295 of heavy chain. The non-glycosylated sutimlimab has an overall molecular weight of approximately 144,813 Da.

- Mechanism of Action (MoA):
  Binding of C1 complex to cold agglutinins (generally IgM isotype) which bind to the I antigen uniformally present on the surface of all RBCs activates classical complement pathway and leads to RBCs hemolysis. C1s is a critical component of C1 complex. Sutimlimab binds to C1s, then inhibits C1 complex induced classical complement pathway and subsequently reduce RBCs hemolysis.

- Potency Assays:
  - An ELISA binding assay is used to determine the relative binding activity of the sutimlimab to the purified recombinant human active C1s antigen. Specifically, C1s antigen is first coated into a 96-well plate. After saturation, the plate is incubated with different dilutions of sutimlimab. The antibody/antigen interaction is revealed with a secondary antibody targeting human IgG conjugated to horse radish peroxidase (HRP). After incubation with tetramethylbenzidine (TMB) substrate the colorimetric signal reveals the binding of sutimlimab to the C1s antigen. The reaction is then stopped using an acid. The serial dilution of sutimlimab allows for the generation of a dose response curve for samples. EC50 values are then obtained from the four-parameter logistic dose response curves and used to generate a relative potency value by dividing the reference EC50 by the sample EC50.

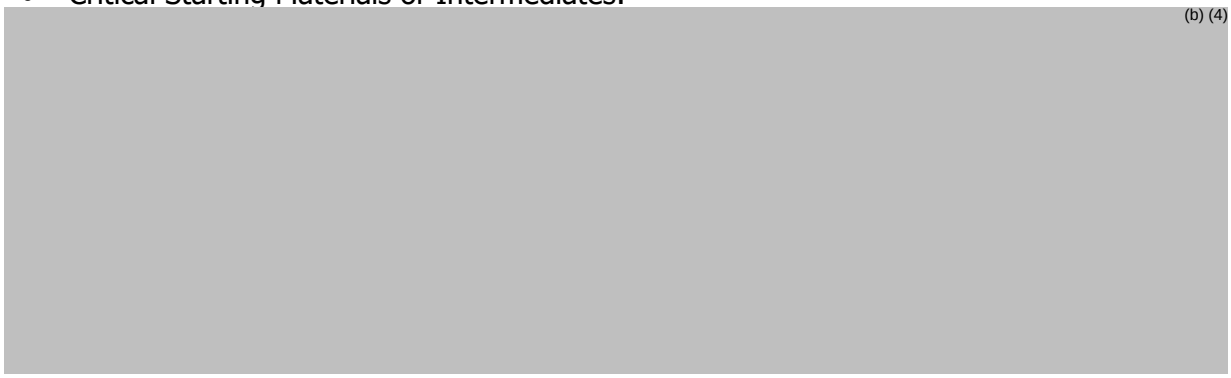
  - The Wieslab complement assay is an ELISA based assay used to determine the relative activity of the sutimlimab blocking the formation of MAC when a classical complement pathway is activated. Specifically, IgM is first coated into a 96-well plate. The plate is then incubated with different dilution of sutimlimab diluted with 1% Normal Human Serum (NHS) and diluent containing a specific blocker to ensure that only the classical complement pathway is activated. The newly formed MAC binds with specific alkaline phosphatase-labeled antibody. Moreover, detection of specific antibodies is obtained by incubation with alkaline phosphatase substrate solution (i.e., p-nitrophenyl phosphate (pNPP)). The amount of complement activation corelates with the color intensity and is measured in terms of absorbance.

- Reference Materials:
  Sutimlimab has received the FDA Orphan Drug Designation for autoimmune hemolytic anemia (including CAD) and has been granted a Breakthrough Therapy Designation in the US for the treatment of hemolysis in patients with primary CAD. (b) (4)

(b) (4)

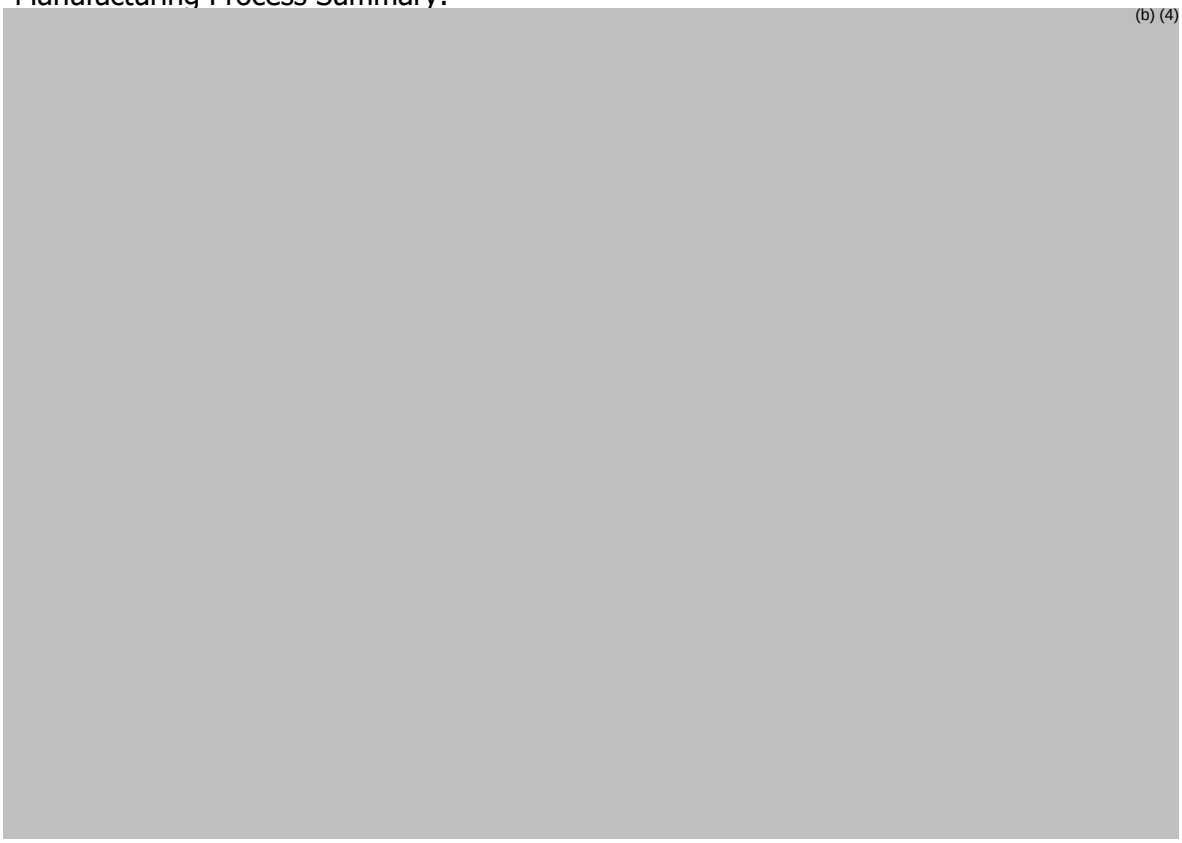
- Critical Starting Materials or Intermediates:

(b) (4)



- Manufacturing Process Summary:

(b) (4)



(b) (4)

- Container Closure System:
  (b) (4)
  The CCS is suitable for sutimlimab, based on stability data and maintenance of closure integrity.

- Dating Period and Storage Conditions:
  The dating period (b) (4) months when stored at (b) (4) °C.

C. Drug Product (Sutimlimab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety (pyrogenic fever), Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity		N/A
Container closure integrity (contaminant)	Safety (failure in closure integrity may lead to contamination and loss of sterility or evaporation/leakage	Container closure breaches during storage		N/A

	impacting concentration or content)			
Quantity	Efficacy	Manufacturing process	(b) (4)	N/A
Appearance (Degree of opalescence, color, visible particles) (Product and process related impurities)	Safety, Immunogenicity and stability	Manufacturing material, Formulation components, stability and CCS		N/A
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles		N/A
Polysorbate 80 Concentration	Efficacy (Product oxidation) and Stability	Formulation component		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Extractable volume (General)	Efficacy/Dosing	Fill process		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		Currently, the data from 12 month time point is submitted and acceptable

- Potency and Strength:
  Sutimlimab is supplied as 50 mg/mL solution in one strength (i.e., 1100 mg/22 mL). Potency is defined as the percent activity relative to the current sutimlimab primary reference standard. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:
  Sutimlimab is supplied as a sterile, single-dose, preservative-free solution for intravenously infusion in one strength. Each vial of 1100 mg/22 mL strength is filled with a target fill volume of (b) (4) mL.

- List of Excipients:
  10 mM sodium phosphate, 140 mM sodium chloride, pH 6.1, 0.02% (w/v) polysorbate 80, water for injection, pH 6.1.

- Reference Materials:
  The same reference standards are used (b) (4).

- Manufacturing Process Summary:

(b) (4)

- Container Closure System:
  The primary CCS for sutimlimab DP consists of a clear (b) (4) 25mL glass vial closed with a (b) (4) rubber stopper (b) (4) The rubber stopper is crimped to the vial with an aluminum overseal with (b) (4) cap.

- Dating Period and Storage Conditions:
  The dating period for the 1100 mg/22 mL strength DP is 18 months when stored at 2-8°C.

- List of Co-Package Components (if applicable): None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not freeze
- Do not shake
- Discard unused portion

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture In-process testing	(b) (4)		Approve	PLI Waived	Approve based on Waiver granted by OPMA/OBP

Release testing (only bioburden and endotoxin)					
Drug substance manufacture In-process testing Release and stability testing (all tests, except container closure integrity)	(b) (4)		Withhold	5 citations associated with failures of the quality unit and failure to follow SOPs.	Withhold based on the deficiencies identified during the inspection and the (b) (4) relevant responses
In-process testing (unprocessed bulk harvest)			Approve	Approved based on profile	Approved based on profile
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacturing, in-process testing, visual inspection	(b) (4)		Approve	PLI Waived	Approve based on Waiver granted by OPMA/OBP
Quality control testing (in-process bioburden, and release for endotoxins and sterility) DP visual inspection			Approve based on profile	N/A	Approve
Container closure integrity testing			Approve based on profile	N/A	Approve
Quality control testing (in-process bioburden, and release for endotoxin and sterility) DP visual inspection			Approve based on profile	N/A	Approve
Secondary packaging and labeling			No Evaluation Necessary	N/A	No Evaluation Necessary

Visual Inspection, Warehousing	(b) (4)	Approve based on profile	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4), proposed for sutimlimab DS and DP manufacture, respectively. All proposed manufacturing for these two facilities is acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

DS manufacturing facility at (b) (4) has never been inspected before by FDA for commercial biotech DS manufacturing, and data integrity issues were identified at (b) (4) regarding stability samples during the BLA review cycle. A PLI of (b) (4) was conducted (b) (4)-(b) (4) by OPQ inspection team. Training, Quality, Materials, Facilities/Equipment, Production, and Laboratory Systems were examined. At the conclusion, 5-item FDA 483-form was issued citing deficiencies. The initial recommendation of the inspection was a "withhold/official action indicated (OAI)". The firm agreed with all observations and committed to a response. The Agency received the responses from (b) (4) to address the deficiencies cited in a 483-form on (b) (4) Due to the insufficient responses from (b) (4), OPMA had a teleconference with (b) (4) on (b) (4) Based on the information provided by (b) (4) OPMA determined that the overall information provided by (b) (4) is unable to conclude that the deficiencies observed in (b) (4) site can be resolved during the current review cycle. The final recommendation of the (b) (4) facility from OPMA is withhold.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
(b) (4)			

(b) (4)

ii. Outstanding review issues/residual risk: During the PLI of the (b) (4) (b) (4) facility from (b) (4) through (b) (4) for this BLA, the inspection team observed objectionable conditions at the facility, issued a 483-form and conveyed the observations to the representative of the facility at the close of the inspection. The responses from (b) (4) to address the facility deficiencies are insufficient, and the Agency is unable to conclude that the deficiencies observed in (b) (4) site can be resolved during the current review cycle for the application.

iii. Future inspection points to consider: (b) (4)

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
(b) (4)			

(b) (4)

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/Source Material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/Source Material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal Source			X	
9.	Transgenic Plant Source			X	
10.	New Molecular Entity		X		
11.	PEPFAR Drug			X	
12.	PET Drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				X
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN Assigned Name		X		
20.	Other [fill in]				X
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in Lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				X

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YAN WANG
01/21/2022 06:22:28 PM

First Approval for Indication: Yes

Recommendation: Pending the final determination of compliance status of the quality control testing site at (b) (4)

BLA 761164
Review Number: 2
Review Date: January 6, 2022

Drug Name/Dosage Form	Enjaymo (sutimlimab-jome) injection (solution)
Strength/Potency	1100 mg/22 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of hemolysis in adult patients with cold agglutinin disease
Applicant	Bioverativ USA Inc. (A Sanofi Company)

Product Overview

Sutimlimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody specific for complement component 1, s subcomponent (C1s) esterase produced in mammalian (Chinese hamster ovary-CHO) cells. Sutimlimab binds to C1s and inhibit the activation of a classical complement pathway, consequently inhibiting the production of membrane attack complex (MAC) that is responsible for red blood cells (RBC) lysis. Sutimlimab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains 1100 mg/22 mL of sutimlimab at concentration of 50 mg/mL with pH of 6.1. Each mL of solution contains 50 mg sutimlimab, 1.13 (b) (4) mg sodium phosphate monobasic monohydrate, 0.48 (b) (4) mg sodium phosphate dibasic heptahydrate, 8.18 (b) (4) mg sodium chloride, 0.2 mg polysorbate 80 and water for injection. The recommended dose for sutimlimab is 6500 mg for patients weighing 39 kg to less than 75 kg, or 7500 mg for patients weighing 75 kg or more administered intravenously once per week for the first two doses followed by every two weeks dosing thereafter.

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	James Barlow and Jennifer Kim Xiaoshi Wang	OPQ/OBP OPQ/OBP/DBRRII
Facility	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Microbiology	Candace Gomez-Broughton	OPQ/OPMA/DBM/BMB2
Team Lead	Yan Wang (product quality) Madushini Dharmasena (microbiology and facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Hamet Toure and Melinda Bauerlien	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Maureen DeMar	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH
Pharm/Tox	Shaji Theodore/ Pedro DelValle	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaolei Pan/Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Enjaymo
   b. Trade Name: ENJAYMO™
   c. Non-Proprietary Name/USAN: Sutimlimab
   d. CAS Registry Number: 2049079-64-1
   e. Common Name: Humanized IgG4 monoclonal antibody, anti-(human complementC1s) (humanized mousemonoclonalTNT009γ4-chain) disulfide with humanized mousemonoclonalTN009k-chain, dimer
   f. INN Name: Sutimlimab
   g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   h. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761164/SN0043 (Re-submission)	August 5, 2021
STN 761164/SN0045 (Information request response)	November 9, 2021 (OBP)

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:
   Refer to the Integrated Quality Assessment (Also referred to as Executive Summary) dated November 11, 2020 for an assessment of Drug Master Files (DMF) and supporting documents referenced in the original BLA.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	128190	Parent IND

3. Consults: None

4. Environmental Assessment:
   Bioverativ USA Inc. claimed a categorical exclusion from the preparation of an environmental assessment for sutimlimab in accordance with 21 CFR 25.31 (c). The claim is based on that sutimlimab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when sutimlimab is exposed to the environment, it would not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist.

   The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc. is pending the final determination of compliance status of the quality control testing site at (b) (4) . FDA assessment of the ability of this facility to conduct quality control tests in compliance with CGMP is required to support approval of the application. This memo documents the review of BLA resubmission in response to a Complete Response (CR) Letter issued on November 13, 2020. The application was not approved in the first review cycle due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of (b) (4) drug substance manufacturing facility (b) (4) From product quality and microbiology perspective, the Office of Biotechnology Products (OBP), OPQ, CDER, and the Office of Pharmaceutical Manufacturing Assessment (OPMA), OPQ, CDER, respectively, did not identify any deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ USA Inc in the first review cycle. In the BLA resubmission, the Applicant removes the (b) (4) site as the drug substance manufacturing facility but keeps (b) (4) site for quality control testing for both drug substance and drug product. The on-site PLI led by the office of Regulatory Affairs (ORA) will start on (b) (4) . The final determination of compliance status of the quality control testing site at (b) (4) is pending on the inspectional outcome.

Manufacturing and control strategy updates made since the first review cycle were included in the response to the CR Letter and reviewed. The product quality information provided in the resubmission does not impact the recommendation of approval for BLA 761164 made by OBP during the first review cycle. The data submitted in the original application and subsequent resubmission are adequate to support the conclusion that the manufacture of Enjaymo (sutimlimab-jome) is well controlled and leads to a product that is pure and potent. Therefore, OPQ recommends that this product be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance:
  (b) (4)
- Drug Product:
  (b) (4)

- Fill size and dosage form: 1100 mg/22 mL solution

- Dating period:
  - Drug Product: 18 months at 2-8°C
  - Drug Substance: (b) (4) months at (b) (4) °C
  - Stability Option:
    - Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
    - For stability protocols: We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release in accordance with 21 CFR 601.2a. Enjaymo (sutimlimab-jome) is a specified product.

C. Benefit/Risk Considerations:

Refer to the Executive Summary memo dated November 11, 2020 for Benefit/Risk Considerations assessed during the first review cycle.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

(b) (4)

II. Summary of Quality Assessments:

Refer to the Executive Summary memo dated November 11, 2020 for an assessment of critical quality attributes, risks, lifecycle management, and establishment information. Additional information is in the Product Quality, Microbiology, and Facility primary technical reviews.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YAN WANG
01/06/2022 06:50:32 PM

BLA STN 761164
Resubmission

ENJAYMO™ (Sutimlimab)

Bioverativ USA, Inc.

Xiaoshi Wang, Ph.D., Primary Assessor
Yan Wang, Ph.D., Team Lead

Division of Biotechnology Review & Research II (DBRR II)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. BLA#: 761164

2. Review Date: December 21, 2021

3. Primary Review Team:
   a. **Medical Officer**: Carrie Diamond, Tanya Wroblewski (CDTL)
   b**. Pharm/Tox**: Shaji Theodore and Pedro DelValle
   c. **Product Quality Team**:
      OPQ/OBP: Xiaoshi Wang, Yan Wang (ATL)
      OPQ/OPMA: Candace Gomez-Broughton (Micro and Facility), Madushini Dharmasena (Micro and Facility TL)
      OPQ/OBP (labeling): James Barlow
      OPQ/RBPM: Hamet Toure and Melinda Bauerlien
   d. **Clinical Pharmacology**: Xiaolei Pan; Sudharshan Hariharan
   e. **Statistics**: Yeh-Fong Chen
   f. **OND RPM**: Maureen DeMar

4. Major GRMP Deadlines:
   a. BLA planning meeting: 08/24/2021
   b. Mid-cycle internal meeting: 11/2/2021
   c. Late-cycle internal meeting: 12/15/2021
   d. Primary review due: 1/4/2022
   e. Secondary review due: 1/7/2022
   i. PDUFA action date: 2/5/2022 (Class 2 resubmission)

5. Communications and submissions:

Communication/Document	Date	Submission	Review status
BLA resubmission		STN 761164/SN 0043, 08/05/2021	Complete
Information Request #1	11/2/2021	STN 761164/SN 0045, 11/9/2021	Complete

6. Drug Product Name/Code/Type:
   a. Proprietary Name: ENJAYMO
   b. Trade Name: ENJAYMO™
   c. Non-Proprietary Name/USAN: Sutimlimab
   d. CAS Registry Number: 2049079-64-1
   e. Common Name: Immunoglobulin G4, anti-(human complement C1s) (humanized mouse monoclonal TNT009 γ4-chain), disulfide with humanized mouse monoclonal TNT009 k-chain, dimer
   f. INN Name: Sutimlimab
   g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   h. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

7. Pharmacological Category: a humanized IgG4 monoclonal antibody that targets the classical complement pathway specific serine protease, complement component 1, s subcomponents (C1s) and

inhibits the classical complement pathway, for the treatment of hemolysis in cold agglutinin disease (CAD).

8. Dosage Form: Solution for injection in a single dose vial

9. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 1100 mg/22 mL
   (ii): Type of potency assay(s): two potency assays are proposed for the commercial release and stability testing of BIVV009 drug substance (DS) and drug product (DP). First potency assay is a ligand binding ELISA that measures the first binding step between BIVV009 with C1s. The second potency assay is a plated based, classical complement pathway specific assay that measures the inhibition of C5b-C9 membrane attack complex (MAC) formation in the classical complement pathway caused by C1s binding with BIVV009.

10. Route of Administration: Intravenous infusion

11. Referenced Drug Master Files (DMF):
Refer to the first cycle primary technical review dated October 13, 2020.

12. Inspectional Activities:
An Office of Regulatory Affairs (ORA) led on-site pre-license inspection (PLI) for the quality control testing site at (b) (4) will begin on (b) (4) We defer the final recommendation for the facility to ORA and OPMA.

In the initial BLA submission, the PLI was waived for DS manufacturing facility at (b) (4) and DP manufacturing facility at (b) (4)

13. Consults Requested by OBP: NA

14. Quality by Design Elements: The following was submitted in the identification of QbD elements
Refer to the first cycle primary technical review dated October 13, 2020.

15. Precedents: None.

16. Administrative:

Signature Block

Name and Title	Signature and Date
Yan Wang, Ph.D. Team Lead, DBRRII/OBP/OPQ/CDER	See electronic signature and date
Xiaoshi Wang, Ph.D. Primary assessor, DBRRII/OBP/OPQ/CDER	See electronic signature and date

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation:
The data submitted in this Biologics License Application (STN 761164) support the conclusion that the manufacture of ENJAYMO™ (sutimlimab) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from multiple production runs. From product quality perspective, it is recommended that ENJAYMO™ (sutimlimab) be approved for human use under conditions specified in the package insert.

The assessment of DS and DP microbiology and facility including the acceptability of the Pre-License Inspection (PLI) of (b) (4) is deferred to CDER, Office of Pharmaceutical Quality (OPQ), Office of Pharmaceutical Manufacturing Assessment (OPMA).

II. List of Deficiencies to be Communicated: None

III. List of Post-Marketing Commitments/Requirements:

(b) (4)

IV. Review of Common Technical Document - Quality Module 1:
Environmental Assessment of Claim of Categorical Exclusion
The Applicant claims a categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR §25.15(d) under the provisions of 21 CFR 25.31(b and c). Thus, no environmental assessment needs to be performed. Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review:
The carton and container labels are assessed by OBP. The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

VI. Review of Common Technical Document - Quality Module 3.2 and Module 2.3 Quality Overall Summary Refer to technical review for the first review cycle dated October 13, 2020 and the review below.

VII. Review of Immunogenicity Assays
Refer to technical review for the first review cycle dated October 13, 2020 and the review below.

TABLE OF CONTENTS

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Xiaoshi Wang

Digitally signed by Xiaoshi Wang
Date: 12/21/2021 11:25:57AM
GUID: 5acb8a0d000ff95628573aa8ecd8547d

Yan Wang (OPQ/OBP)

Digitally signed by Yan Wang (OPQ/OBP)
Date: 12/21/2021 12:15:37PM
GUID: 508da7420002bb89a21873bfe63d2afd

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY ASSESSMENT AND EVALUATION

ASSESSOR: Maria Gema Martin Manso, Ph.D.
SECONDARY ASSESSOR: Reyes Candau-Chacon, Ph.D.

BLA:	761164
Applicant:	Bioverativ USA, Inc.
US License Number:	2078
Submission:	BLA 351(a)
Product:	Enjaymo (sutimlimab, IgG4, anti-human complement C1s)
Indication:	For the treatment of hemolysis in adult patients with cold agglutinin disease (CAD) Orphan Designation No.: 15-5061
Dosage Form:	Solution for injection, 1,100 mg/22 mL (50 mg/mL); (b) (4) mm vial; single use; intravenous infusion administration.
Manufacturing Site (Drug Product):	(b) (4)
FDA Receipt Date:	03/13/2020
Action Date:	11/13/2020

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval.

34 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

First Approval for Indication
Recommendation: Compete Response

BLA Number: 761164
Review Number: 1
Review Date: November 6, 2020

Drug Name/Dosage Form	Enjaymo (sutimlimab-jome) injection (solution)
Strength/Potency	1100 mg/22 mL
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment of hemolysis in adult patients with cold agglutinin disease
Applicant/Sponsor	Bioverativ UAS Inc. (A Sanofi Company)

Product Overview

Sutimlimab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody specific for complement component 1, s subcomponent (C1s) esterase produced in mammalian (Chinese hamster ovary-CHO) cells. Sutimlimab binds to C1s and inhibit the activation of a classical complement pathway, consequently inhibiting the production of membrane attack complex (MAC) that is responsible for red blood cells (RBC) lysis. Sutimlimab drug product (DP) is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each DP vial contains 1100 mg/22 mL of sutimlimab at concentration of 50 mg/mL with pH of 6.1. Each mL of solution contains 50 mg sutimlimab, 1.13 (b)(4) mg sodium phosphate monobasic monohydrate, 0.48 (b)(4) mg sodium phosphate dibasic heptahydrate, 8.18 (b)(4) mg sodium chloride, 0.2 mg polysorbate 80 and water for injection. The recommended dose for sutimlimab is 6500 mg for patients weighing 39 kg to less than 75 kg, or 7500 mg for patients weighing 75 kg or more administered intravenously once per week for the first two doses followed by every other week dosing thereafter.

Quality Review Team

Discipline	Reviewer	Office/Branch/Division
Product Quality (Drug Substance (DS) and DP)/Immunogenicity Assay	Xiaoshi Wang	OPQ/OBP/DBRRII
Labeling	Scott Dallas James Barlow Xiaoshi Wang	OPQ/OBP OPQ/OBP OPQ/OBP/DBRRII
Facility	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Microbiology	Viviana Matta (DS) Maria (Gema) Martin Manso (DP)	OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2
Inspection	Viviana Matta (lead) Cyrus Agarabi	OPQ/OPMA/DBM/BMB2 OPQ/OBP/DBRRII
Team Lead	Yan Wang (product quality) Candace Gomez-Broughton (microbiology, DS) Maria (Reyes) Candau-Chacon (microbiology, DP) Peter Qiu (facility)	OPQ/OBP/DBRRII OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM/BMB2 OPQ/OPMA/DBM
Application Team Lead	Yan Wang	OPQ/OBP/DBRRII
OBP Review Chief	Xianghong (Emily) Jing	OPQ/OBP/DBRRII
RBPM	Florence Aisida	OPQ/OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Maureen DeMar/Charlene Wheeler	OND/OCHEN/DNH
Cross-disciplinary Team Lead	Tanya Wroblewski	OND/OCHEN/DNH
Medical Officer	Carrie Diamond	OND/OCHEN/DNH
Pharm/Tox	Shaji Theodore/Lee Elmore	OND/OCHEN/DPTCHEN
Clinical Pharmacology	Xiaolei Pan/Sudharshan Hariharan	OTS/OCP/DCEP
Statistics	Yaping Wang/Yeh-Fong Chen	OTS/OB/DBIX

1. Names:
   a. Proprietary Name: Enjaymo
   b. Trade Name: ENJAYMO™
   c. Non-Proprietary Name/USAN: Sutimlimab
   d. CAS Registry Number: 2049079-64-1
   e. Common Name: Humanized IgG4 monoclonal antibody, anti-(human complementC1s) (humanized mousemonoclonalTNT009γ4-chain) disulfide with humanized mousemonoclonalTN009k-chain, dimer
   f. INN Name: Sutimlimab
   g. OBP systematic name: MAB HUMANIZED (IGG4) ANTI P09871 (C1S_HUMAN) [BIVV009]
   h. Other name(s): BIVV009 (company code), Anti-C1s VH4/Vk2, TNT009, (b) (4)

Submissions Reviewed:

Submission(s) Reviewed	Document Date (disciplines affected)
STN 761164/SN0001 (Pre-submission)	September 5, 2019 (Non-clinical submission)
STN 761164/SN0001 (Pre-submission)	February 28, 2020 (Clinical submission)
STN 761164/SN0003 (Original submission)	March 13, 2020 (OBP and OPMA)
STN 761164/SN0004 (Quality submission within 30 days for Photostability, temperature excursion and in-use data)	April 10, 2020 (OBP and OPMA)
STN 761164/SN007 (Quality submission for data integrity investigation deviation reports)	May 1, 2020 (OBP and OPMA)
STN 761164/SN0009 (Information request (IR) response)	May 19, 2020 (OPMA)
STN 761164/SN0010 (IR response)	May 28, 2020 (OBP)
STN 761164/SN0013 (IR response)	June 12, 2020 (OBP)
STN 761164/SN0014 (IR response)	July 2, 2020 (OBP)
STN 761164/SN0015 (IR response)	July 9, 2020 (OBP)
STN 761164/SN0016 (IR response)	July 20, 2020 (OBP)
STN 761164/SN0017 (IR response)	July 17, 2020 (OPMA)
STN 761164/SN0018 (IR response)	July 28, 2020 (OBP)
STN 761164/SN0019 (IR response)	August 4, 2020 (OPMA)
STN 761164/SN0020 (IR response)	August 5, 2020 (OBP)
STN 761164/SN0021 (IR response)	August 10, 2020 (OBP)
STN 761164/SN0024 (IR response)	August 31, 2020 (OPMA)
STN 761164/SN0025 (IR response)	September 2, 2020 (OBP)
STN 761164/SN0027 (IR response)	September 15, 2020 (OBP)
STN 761164/SN0028 (IR response)	September 18, 2020 (OPMA)
STN 761164/SN0029 (IR response)	September 25, 2020 (OBP and OPMA)
STN 761164/SN0030 (IR response)	October 1, 2020 (OBP)
STN 761164/SN0032 (IR response)	October 5, 2020 (OBP)
STN 761164/SN0033 (IR response)	October 9, 2020 (OBP)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	3	Adequate	N/A	N/A
	V			2	Adequate	(b) (4)	N/A
	III			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A
	II			3	Adequate	N/A	N/A

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	128190	Parent IND

3. Consults: None

4. Environmental Assessment:

   Bioverativ USA Inc. claimed a categorical exclusion from the preparation of an environmental assessment for sutimlimab in accordance with 21 CFR 25.31 (c). The claim is based on that sutimlimab is comprised of linked naturally occurring amino acid chains which are significantly metabolized *in-vivo* and expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. Therefore, when sutimlimab is exposed to the environment, it would not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. No extraordinary circumstances exist.

The claim of a categorical exclusion is accepted.

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation:

This application will not be approved during this assessment cycle due to deficiencies identified for (b) (4) facility. The Office of Pharmaceutical Manufacturing Assessment (OPMA), Office of Pharmaceutical Quality (OPQ), CDER is recommending that the application not be approved due to deficiencies related to readiness for commercial manufacturing and data integrity that were observed at the FDA pre-license inspection (PLI) of the (b) (4) drug substance manufacturing facility (b) (4) From a product quality perspective, the Office of Biotechnology Products (OBP), OPQ, CDER, does not note any product quality deficiencies that would preclude approval of STN 761164 for Enjaymo (sutimlimab-jome) manufactured by Bioverativ UAS Inc at this time. Because the application will not be approved in this cycle, the manufacturing facility issues listed below will be directly communicated to (b) (4) due to (b) (4) is a contract manufacturing organization (CMO). If manufacturing changes are made before the applicant submits their responses to the complete response (CR) deficiencies, additional assessment may be needed during the next assessment cycle.

B. Summary of Complete Response Issues:

The following deficiencies were identified regarding (b) (4) facility which is responsible for sutimlimab DS manufacturing process and quality control for release and stability testing of sutimlimab DS and DP.

A PLI was conducted at the (b) (4) facility in (b) (4). The PLI resulted in a final withhold decision for this BLA.

- Lack of quality oversight
- Significant data integrity concerns and failure to conduct a comprehensive data integrity assessment to ensure the accurate and reliable results submitted to the BLA application

C. Complete Response Letter Draft Language:

During a recent inspection of the (b) (4) facility for this BLA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

D. Benefit/Risk Considerations:

Cold agglutinin disease (CAD) is a type of autoimmune hemolytic anemia caused by IgM-induced complement pathway activation. The disease is characterized by the presence of

autoantibodies called cold agglutinins (generally IgM isotype and act as potent activators of the complement pathway) that typically bind to the I antigen uniformally present on the surface of all RBCs. Sutimlimab is a humanized IgG4 monoclonal antibody and it specifically targets C1s. Sutimlimab blocks the activity of the C1s esterase, the proximal step in the activation of the classical complement pathway. Inhibition of C1s has been shown to inhibit RBC opsonization and downstream complement activity, protection of RBCs from hemolytic clearance and destruction. There is a high unmet medical need for treatment of hemolysis in CAD which leads to severe symptomatic anemia because no therapies are currently approved for the treatment of patients with CAD.

Review of manufacturing has identified that the methodologies used for DS and DP manufacturing, release and stability testing are sufficiently controlled to result in a consistent and safe product from product quality perspective. In addition, the microbial control and sterility assurance strategy are sufficient to support consistent manufacture of a sterile product from microbiology product quality perspective. The proposed commercial manufactures of sutimlimab DS at (b) (4) and of sutimlimab DP at (b) (4) (b) (4) are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage. However, due to the deficiencies identified in the proposed commercial DS manufacturing facility as well as the quality control testing unit at (b) (4) site, the Agency is unable to conclude that the (b) (4) facility is ready for commercial manufacturing and can adequately resolve data integrity issues during the current review cycle for the application. The OBP product quality and immunogenicity assay, OPMA facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

(b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management for Sutimlimab

Table 1: Active Pharmaceutical Ingredient CQA (critical quality attribute) Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes

Binding to C1s (Potency)	Efficacy	Intrinsic to the molecule, impacted by oxidation and low pH stress	Characterized by a C1s binding assay (ELISA, (b) (4) Characterized by reduced FcγR and C1q binding affinities
Production of MAC (Potency)	Efficacy	Intrinsic to the molecule	Characterized by a Wieslab complement assay (b) (4)
Inhibition of sheep red blood cell hemolysis (Potency)	Efficacy	Intrinsic to the molecule	Characterized by a cell-based assay (b) (4)
Identity	Efficacy and Safety	Intrinsic to the molecule	N/A
High Molecular Weight (HMW) species/Aggregates (Product related impurity)	Pharmacokinetics (PK), and Safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low pH, high pH, oxidation reagent stress, metals (b) (4) and light	(b) (4)
LMW species/Fragments (Product related impurity)	Efficacy	Manufacturing process, and exposure to low pH, high pH, heat and oxidation reagent stress, metals (b) (4) and light	N/A
Heavy chain (b) (4)	PK	Manufacturing process and exposure to oxidation reagent stress and photo stress Minimal change is expected on stability due	(b) (4)

		to high temperature and pH stress Significant increased under photo stress		
High mannose	PK	Bioreactor conditions Minimal change is expected on stability	(b) (4)	
Charge variant profile (Acidic variants)	Efficacy, PK/ Pharmacodynamics (PD)	Manufacturing process and exposure to high pH, oxidation reagent stress, metal (b) (4) and light		
Charge variant profile (Basic variants)	Efficacy, PK/PD	Manufacturing process and exposure to heat, low pH, high pH, oxidation reagent stress, metals (b) (4) and light		

B. Drug Substance (Sutimlimab) Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
(b) (4) Concentration	Efficacy (Product oxidation) and Stability	(b) (4)	(b) (4)	N/A
Quantity	Efficacy	Manufacturing process		N/A
pH (General)	Efficacy and Stability	(b) (4) and stability		N/A
Osmolality (General)	Stability	Composition of the DS		N/A
Appearance (Includes degree of opalescence and color of solution) (General)	Stability	(b) (4) and stability		N/A
Host Cell DNA (Process related impurity)	Safety	Production cell line, bioreactor (b) (4)		(b) (4)
Host Cell Protein (Process related impurity)	Immunogenicity	Production cell line, bioreactor (b) (4)		

		(b) (4)	(b) (4)	(b) (4)
(b) (4) (Process related impurity)	Safety	Purification through the (b) (4)		
Adventitious viruses, endogenous virus (Process related impurity)	Safety	Cell banks, raw materials		
Mycoplasma (Process related impurity)	Safety	Cell banks, raw materials		
Endotoxin (contaminant)	Safety and Purity	Raw materials and manufacturing process		N/A
Bioburden (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Raw materials and manufacturing process		N/A
Leachables (Process-related impurity)	Safety and Stability	From manufacturing contact material and the DS container closure system (CCS)		N/A
(b) (4)	Safety	(b) (4)		Levels are below toxicological concern based on the risk assessment

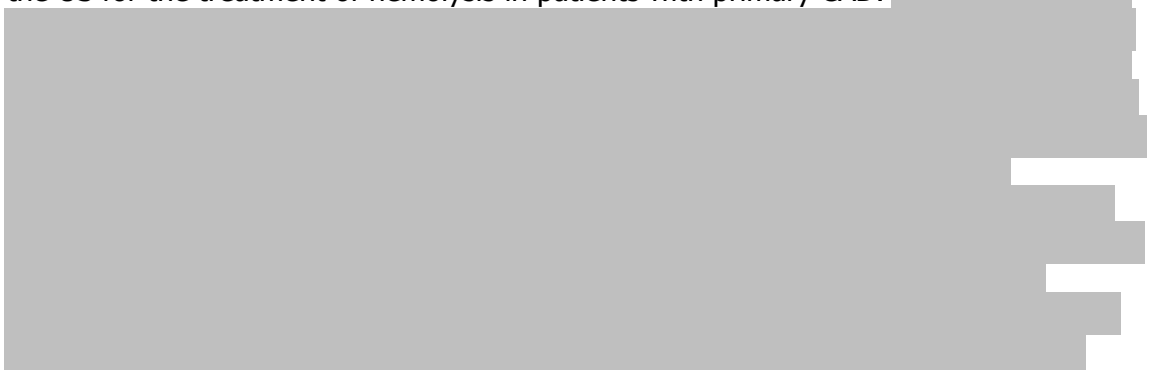
- Description:
  Sutimlimab is a humanized IgG4 monoclonal antibody (mAb) against C1s. Sutimlimab is produced from a mammalian cell line (CHO) using a fed-batch production process. Sutimlimab is composed of two identical immunoglobulin kappa light chains and two identical immunoglobulin gamma heavy chains. Sutimlimab contains a serine-to-proline mutation (S241P) for stabilization of the core-hinge region of the molecule. In addition, sutimlimab contains a leucine-to-glutamic acid mutation (L248E) to reduce Fcγ receptor binding. Sutimlimab contains 32 cysteines leading to 16 disulfide bonds and two glycosylation sites located on Asparagine N295 of heavy chain. The non-glycosylated sutimlimab has an overall molecular weight of approximately 144,813 Da.

- Mechanism of Action (MoA):
  Binding of C1 complex to cold agglutinins (generally IgM isotype) which bind to the I antigen uniformally present on the surface of all RBCs activates classical complement pathway and leads to RBCs hemolysis. C1s is a critical component of C1 complex. Sutimlimab binds to C1s, then inhibits C1 complex induced classical complement pathway and subsequently reduce RBCs hemolysis.

- Potency Assays:
  - An ELISA binding assay is used to determine the relative binding activity of the sutimlimab to the purified recombinant human active C1s antigen. Specifically, C1s antigen is first coated into a 96-well plate. After saturation, the plate is incubated with different dilutions of sutimlimab. The antibody/antigen interaction is revealed with a secondary antibody targeting human IgG conjugated to horse radish peroxidase (HRP). After incubation with tetramethylbenzidine (TMB) substrate the colorimetric signal reveals the binding of sutimlimab to the C1s antigen. The reaction is then stopped using an acid. The serial dilution of sutimlimab allows for the generation of a dose response curve for samples. EC50 values are then obtained from the four-parameter logistic dose response curves and used to generate a relative potency value by dividing the reference EC50 by the sample EC50.

  - The Wieslab complement assay is an ELISA based assay used to determine the relative activity of the sutimlimab blocking the formation of MAC when a classical complement pathway is activated. Specifically, IgM is first coated into a 96-well plate. The plate is then incubated with different dilution of sutimlimab diluted with 1% Normal Human Serum (NHS) and diluent containing a specific blocker to ensure that only the classical complement pathway is activated. The newly formed MAC binds with specific alkaline phosphatase-labeled antibody. Moreover, detection of specific antibodies is obtained by incubation with alkaline phosphatase substrate solution (i.e., p-nitrophenyl phosphate (pNPP)). The amount of complement activation corelates with the color intensity and is measured in terms of absorbance.

- Reference Materials:
  Sutimlimab has received the FDA Orphan Drug Designation for autoimmune hemolytic anemia (including CAD) and has been granted a Breakthrough Therapy Designation in the US for the treatment of hemolysis in patients with primary CAD. (b) (4)



(b) (4)

- Critical Starting Materials or Intermediates:

(b) (4)

- Manufacturing Process Summary:

(b) (4)

(b) (4)

- Container Closure System:
(b) (4)

- Dating Period and Storage Conditions:
The dating period (b) (4) months when stored at (b) (4) °C.

C. Drug Product (Sutimlimab) Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (Type)	Risk	Origin	Control Strategy	Other Notes
Sterility (contaminant)	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity	(b) (4)	N/A
Endotoxin (contaminant)	Safety (pyrogenic fever), Purity, and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing process or failure of container closure integrity		N/A
Container closure integrity (contaminant)	Safety (failure in closure integrity may lead to contamination and loss of sterility or evaporation/leakage impacting concentration or content)	Container closure breaches during storage		N/A
Quantity	Efficacy	Manufacturing process		N/A
Appearance (Degree of opalescence, color, visible particles) (Product	Safety, Immunogenicity and stability	Manufacturing material, Formulation components, stability and CCS		N/A

and process related impurities)				
Particulate matter for subvisible particles (Product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS, subvisible particles could be product or foreign particles	(b) (4)	N/A
Polysorbate 80 Concentration	Efficacy (Product oxidation) and Stability	Formulation component		N/A
pH (General)	Efficacy and Stability	Formulation components and stability		N/A
Extractable volume (General)	Efficacy/Dosing	Fill process		N/A
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		Currently, the data from 12 month time point is submitted and acceptable

- Potency and Strength:
  Sutimlimab is supplied as 50 mg/mL solution in one strength (i.e., 1100 mg/22 mL). Potency is defined as the percent activity relative to the current sutimlimab primary reference standard. The potency assays are the same as described in the DS section of this memo.

- Summary of Product Design:
  Sutimlimab is supplied as a sterile, single-dose, preservative-free solution for intravenously infusion in one strength. Each vial of 1100 mg/22 mL strength is filled with a target fill volume of (b) (4) mL.

- List of Excipients:
  10 mM sodium phosphate, 140 mM sodium chloride, pH 6.1, 0.02% (w/v) polysorbate 80, water for injection, pH 6.1.

- Reference Materials:
  The same reference standards are used (b) (4).

- Manufacturing Process Summary:
  (b) (4)

(b) (4)

- Container Closure System:
  The primary CCS for sutimlimab DP consists of a clear (b) (4) 25mL glass vial closed with a (b) (4) rubber stopper (b) (4) The rubber stopper is crimped to the vial with an aluminum overseal with (b) (4) cap.

- Dating Period and Storage Conditions:
  The dating period for the 1100 mg/22 mL strength DP is 18 months when stored at 2-8°C.

- List of Co-Package Components (if applicable): None

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:
- Store in a refrigerator at 2°C to 8°C in the original carton
- Protect from light
- Do not freeze
- Do not shake
- Discard unused portion

F. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture In-process testing Release testing (only bioburden and endotoxin)	(b) (4)		Approve	PLI Waived	Approve based on Waiver granted by OPMA/OBP
Drug substance manufacture In-process testing			Withhold	5 citations associated with failures of the quality unit and	Withhold based on the deficiencies identified during the inspection

Release and stability testing (all tests, except container closure integrity)				failure to follow SOPs.	and the (b) (4) relevant responses
In-process testing (unprocessed bulk harvest)	(b) (4)		Approve	Approved based on profile	Approved based on profile
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacturing, in-process testing, visual inspection	(b) (4)		Approve	PLI Waived	Approve based on Waiver granted by OPMA/OBP
Quality control testing (in-process bioburden, and release for endotoxins and sterility) DP visual inspection			Approve based on profile	N/A	Approve
Container closure integrity testing			Approve based on profile	N/A	Approve
Quality control testing (in-process bioburden, and release for endotoxin and sterility) DP visual inspection			Approve based on profile	N/A	Approve
Secondary packaging and labeling			No Evaluation Necessary	N/A	No Evaluation Necessary
Visual Inspection, Warehousing			Approve based on profile	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for sutimlimab DS and DP manufacture, respectively. All proposed manufacturing for these two facilities is acceptable based on their currently acceptable cGMP compliance status and recent relevant inspectional coverage.

DS manufacturing facility at (b) (4) has never been inspected before by FDA for commercial biotech DS manufacturing, and data integrity issues were identified at (b) (4) regarding stability samples during the BLA review cycle. A PLI of (b) (4) was conducted (b) (4) by OPQ inspection team. Training, Quality, Materials, Facilities/Equipment, Production, and Laboratory Systems were examined. At the conclusion, 5-item FDA 483-form was issued citing deficiencies. The initial recommendation of the inspection was a "withhold/official action indicated (OAI)". The firm agreed with all observations and committed to a response. The Agency received the responses from (b) (4) to address the deficiencies cited in a 483-form on (b) (4) Due to the insufficient responses from (b) (4), OPMA had a teleconference with (b) (4) Based on the information provided by (b) (4) OPMA determined that the overall information provided by (b) (4) is unable to conclude that the deficiencies observed in (b) (4) site can be resolved during the current review cycle. The final recommendation of the (b) (4) facility from OPMA is withhold.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
(b) (4)			

(b) (4)

ii. Outstanding review issues/residual risk: During the PLI of the (b) (4) facility from (b) (4) for this BLA, the inspection team observed objectionable conditions at the facility, issued a 483-form and conveyed the observations to the representative of the facility at the close of the inspection. The responses from (b) (4) to address the facility deficiencies are insufficient, and the Agency is unable to conclude that the deficiencies observed in (b) (4) site can be resolved during the current review cycle for the application.

iii. Future inspection points to consider: (b) (4)

b. Drug Product

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
(b) (4)			

ii. Outstanding review issues/residual risk: None
iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				X
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)			X	
17.	End of Phase II/Pre-NDA Agreements tem			X	
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [fill in]				X
	Quality Considerations				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements			X	
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				X

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YAN WANG
11/06/2020 04:10:20 PM

XIANGHONG JING
11/06/2020 04:16:12 PM